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Drug Treatment for PTSD

Answers and Questions

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The first randomized clinical trial of a drug treatment for posttraumatic stress disorder (PTSD) was published in 1988 (ref. 1, later expanded to ref. 2). It was a promising beginning. Good results were obtained with both a monoamine oxidase inhibitor (MAOI) and a tricyclic antidepressant (TCA) in Vietnam veterans with PTSD. Since that time, however, only eight additional clinical trials have been published and only two drugs have been tested more than once. This paucity of drug studies contrasts unfavorably with the proliferation of studies on the neurobiology and psychophysiology of PTSD.

During this same period, a number of neurobiological abnormalities have been detected among PTSD patients, and it appears that we may have only scratched the surface in appreciating the complex pathophysiology of this disorder. Furthermore, unlike the situation with most psychiatric disorders, a number of promising animal models for PTSD provide an opportunity to conduct extensive laboratory testing on potentially useful pharmacological agents before initiating clinical trials.[3]

Although recent findings with fluoxetine[4] have revived hopeful interest in pharmacotherapy for PTSD, we must ask ourselves why progress has been so slow and why success has been so elusive in drug treatment for PTSD. There are a number of related questions: (1) Have we been testing drugs on the wrong clinical populations? (2) Have we optimized our clinical trials with respect to design and instrumentation? (3) Have we been testing the wrong drugs? (4) Are there different subtypes or stages of PTSD that may require different treatments at different times? (5) Is there a magic bullet for PTSD? Before considering these questions, we need to review the current literature on pharmacotherapy for PTSD.

LITERATURE REVIEW

Overview

TABLE 1 presents information from the nine published randomized clinical trials on drug treatment for PTSD. It shows that most studies have tested antidepressants (TCAs, MAOIs, and selective serotonin reuptake inhibitors [SSRIs]), most investigations have been conducted on military veterans, and most outcomes have been assessed with the Impact of Events Scale (IES). Results have been mixed. If you accept the

TABLE 1. Randomized Clinical Trials of PTSD: Drug vs Placebo Treatment[a]

Drug Class	Study[b]	*n*	Subjects	Length (wk)	Outcome	Drugs	Effect Size
TCA	8	46	Military	8	IES Total	Amitriptyline	.38
TCA	20	18	Military	4	IES Avoidance	Desipramine	.04
TCA	20	18	Military	4	IES Intrusion	Desipramine	.16
TCA	2	60	Military	8	IES Total	Imipramine	.39
MAOI	2	60	Military	8	IES Total	Phenelzine	.70
MAOI	5[c]	13	Mil./Civ.	4	IES Total	Phenelzine	−.41
MAOI/SSRI	6	113	Mil./Civ.	10	CAPS Total	Brofaromine	.13
MAOI/SSRI	7	45	Mil./Civ.	14	CAPS Total	Brofaromine	.71
SSRI	4	24	Military	5	PTSD Interview	Fluoxetine	.38
SSRI	4	23	Adult CSA	5	PTSD Interview	Fluoxetine	1.12
BZD	23	10	Mil./Civ.	5	IES Total	Alprazolam	.42
2nd Mess.	28[c]	13	Mil./Civ.	4	IES Total	Inositol	.28

ABBREVIATIONS: TCA = tricyclic antidepressant; MAOI = monoamine oxidase inhibitor; SSRI = selective serotonin reuptake inhibitor; BZD = benzodiazepine; 2nd Mess = second messenger; IES = Impact of Events Scale; CAPS = Clinician Administered PTSD Scale; Mil./Civ. = military and civilian; CSA = childhood sexual abuse.

[a] Augmented and modified from Friedman and Schnurr (1995): Unpublished VA Cooperative Study Research Proposal.

[b] See references.

[c] Cross-over design.

proposition that the minimum effect size necessary for a clinically noticeable difference between an active treatment and a placebo is .5 standard deviations, most drug trials do not exceed this threshold (TABLE 1). This is in marked contrast to randomized clinical psychotherapy trials which have tested exposure therapy or cognitive-behavioral treatments for PTSD in which effect sizes for most studies range between .68 and 1.29 standard deviations (Friedman and Schnurr, 1995, unpublished VA Cooperative Study research proposal).

The three studies with clinically meaningful effect sizes involve an MAOI, phenelzine, an SSRI, fluoxetine, and the novel SSRI/reversible MAO-A inhibitor brofaromine. Even here, however, results are far from unambiguous. Whereas phenelzine had an effect size of .70 in one study,[2] it was less efficacious than placebo (effect size −.41) in another investigation.[5] Whereas fluoxetine had an effect size of 1.12 in adult (mostly female) PTSD patients who had been exposed to childhood sexual abuse, its effect size was only .38 when administered by the same investigators in the same study[4] to adult male Vietnam veterans with war-related PTSD. Finally, whereas brofaromine had an effect size of .71, in one study the effect size was only .13 in a larger multicenter study in which the same protocol was followed.[6,7]

Furthermore, clinical trials with imipramine[2] and amitriptyline[8] demonstrated statistically significant results that may not be clinically meaningful because the effect sizes were only .39 and .38, respectively.

In summary, dramatic responses to medication have been the exception rather than the rule. MAOIs alone or in combination with SSRIs appear more efficacious than other drugs, but serious questions remain about the best way to interpret these positive results.

Selective Serotonin Reuptake Inhibition

SSRIs have revolutionized pharmacotherapy and have replaced TCAs and MAOIs as first line drugs in the treatment of depression, panic disorder, and obsessive compulsive disorder. They also are beginning to emerge as the first choice of clinicians treating PTSD patients despite the few published open trials and only one published randomized clinical trial with an SSRI. In addition, some pharmaceutical companies have begun to show an interest in PTSD treatment as indicated by a large multicenter randomized trial of sertraline currently in progress in both civilian patients and military veterans with PTSD.

In the previously mentioned randomized clinical trial of fluoxetine, van der Kolk and associates[4] observed a marked reduction in overall PTSD symptoms, especially with respect to numbing and arousal symptoms. These results could not be attributed to fluoxetine's antidepressant actions. A particularly important finding (shown in TABLE 1) was the large effect size on adult (mostly female) survivors of childhood sexual abuse (1.12) as compared to a much smaller effect size on military veterans with PTSD (.38). I will return to this point subsequently.

In addition, open trials and case reports on fluoxetine, sertraline, and fluvoxamine have appeared (see ref. 9 for references). Investigators have generally been impressed by the capacity of SSRIs to reduce the numbing symptoms of PTSD, because other drugs tested thus far do not have this property.

A second unique property of SSRIs may make them an attractive choice for PTSD patients, given the high comorbidity rates between PTSD and alcohol abuse/dependence among treatment-seeking patients.[10] Because SSRI treatment has produced significant reductions in alcohol consumption among heavy drinkers and alcohol-dependent subjects.[11] Brady and associates[12] conducted an open trial of sertraline with nine subjects who were comorbid for PTSD and alcohol dependence. They observed significant reductions in both PTSD symptoms and alcohol consumption. This is clearly an important finding that requires more extensive and systematic investigation.

Finally, SSRIs may be clinically useful because a number of symptoms associated with PTSD may be mediated by serotonergic mechanisms. These include rage, impulsivity, suicidal intent, depressed mood, panic symptoms, obsessional thinking, and behaviors associated with alcohol or drug abuse/dependency.[13]

Monoamine Oxidase Inhibitors

Phenelzine produced excellent reduction of PTSD symptoms (effect size .70) during an 8-week randomized clinical trial,[2] but it was less effective than placebo (effect size −.41) in a 4-week cross-over study.[5] The negative findings in the latter study may be explained by differences in study design, differences in duration of treatment, or the unusually high response to placebo[5] which may partially be due to the cross-over design of this study. In addition to these two randomized clinical trials are two successful open trials of phenelzine[14,15] and many positive case reports on MAOI treatment for PTSD (see ref. 16 for references). With one exception, all published results concern phenelzine administration to American or Israeli military veterans with PTSD. The exception is an interesting case report on successful MAOI treatment of five Indochinese refugees with tranylcypromine or isocarboxazid in which remission of PTSD symptoms was invariably associated with amelioration of depressive symptoms.[16]

Southwick *et al.*[17] reviewed all published findings (randomized trials, open trials, and case reports) on MAOI (phenelzine) treatment for PTSD. They found that MAOIs produced moderate to good global improvement in 82% of all patients, primarily because of a reduction in reexperiencing symptoms such as intrusive recollections, traumatic nightmares, and PTSD flashbacks. Insomnia also improved. No improvement was found, however, in PTSD avoidant/numbing, PTSD hyperarousal, depressive, or anxiety/panic symptoms.

In summary, with the exception of Shestatzky *et al.*'s[5] findings in a study that may have been methodologically flawed (see below), MAOIs have effectively reduced PTSD symptoms. Legitimate concerns about the risk of administrating these drugs to patients who may ingest alcohol or certain illicit drugs or who may not adhere to necessary dietary restrictions may be allayed in the future by the use of reversible inhibitors of MAO-A such as moclobemide. The oxidizing action of these drugs is restricted to norepinephrine and serotonin; they are free of hepatotoxicity, and they have a low risk of producing hypertension when combined with tyramine-containing foods.[18]

Brofaromine

Given the favorable results with fluoxetine and phenelzine, a medication that contains the properties of both drugs might be expected to prove effective in PTSD treatment. Brofaromine is such a drug. It is an investigational drug that is both an SSRI and a reversible MAO-A inhibitor. Two multicenter trials have been conducted with brofaromine in which a total of 158 patients were randomized to active drug or placebo groups and in which treatment was continued for 10–14 weeks. Collectively, this is the largest number of patients to have ever received any specific drug and the longest duration of treatment in any randomized clinical trial with PTSD patients. Unfortunately, results with brofaromine have been disappointing. In one study,[6] ($n = 113$), there were essentially no differences between drug and placebo groups after 10 weeks of treatment (effect size was only .13). A better outcome was found in the second study[7] ($n = 45$) in which the effect size was .71 but findings fell short of statistical significance for the overall sample ($p \leq 0.08$). (Results were significant, however [$p \leq 0.05$], when analysis was restricted to patients who had had PTSD for 1 year or more.) Katz and associates[7] argued that their findings should be considered clinically, if not statistically significant, because 55% of patients receiving brofaromine, in contrast to only 26% of those receiving a placebo, no longer met full diagnostic criteria for PTSD following 14 weeks of treatment. They also point out that brofaromine's efficacy was obscured because approximately 30% of placebo patients in both studies exhibited improvement. This contrasts markedly with the low placebo response rates generally observed during randomized clinical trials with PTSD; usually only 5–17% of patients show improvement following placebo treatment.

Tricyclic Antidepressants

There have been three randomized clinical trials with tricyclic antidepressants involving 124 patients as well as numerous case reports and open trials (see ref. 19 for references). As shown in TABLE 1, results have been mixed. Imipramine produced statistically significant global improvement and reductions in reexperiencing symptoms following an 8-week trial, but the effect size was only .39.[2] Amitryptyline significantly reduced avoidant/numbing but not reexperiencing or arousal symptoms after 8 weeks of treatment, but the effect size was only .38.[8] Finally, desipramine was no better than placebo following a 4-week trial.[20] In their analysis of 15 randomized trials, open trials, and case reports involving TCA treatment for PTSD, Southwick and associates[17] found that 45% of patients showed moderate to good global improvement following treatment, whereas MAOIs produced global improvement in 82% of patients who received them. As with MAOIs, most improvement was due to reductions in reexperiencing rather than avoidant/numbing or arousal symptoms. It also appeared that a minimum of 8 weeks of treatment with either TCAs or MAOIs was necessary to achieve positive clinical results. Of interest is a single report on an open trial of clomipramine, a TCA that acts like an SSRI, in which reduction of PTSD reexperiencing symptoms was accompanied by a marked decrease in obsessional symptoms.

To summarize, TCAs appear to reduce PTSD reexperiencing symptoms but have not demonstrated the efficacy of SSRIs or MAOIs.

Benzodiazepines

Although there are theoretical reasons why benzodiazepines might be effective in PTSD[21] and clinical reports that they have been prescribed widely for PTSD patients in some clinical settings,[22] there are only three publications on benzodiazepine treatment for PTSD. In a randomized clinical trial, Braun *et al.*[23] found that alprazolam was no better than placebo in reducing core PTSD symptoms (effect size .42); however, modest reductions in generalized anxiety were observed.

An open trial with alprazolam produced similar results in which PTSD patients reported reduced insomnia, anxiety, and irritability.[24] Finally, Lowenstein,[25] observed that clonazepam successfully reduced insomnia, nightmares, and panic attacks in PTSD patients who also had Dissociative Identity Disorder, but it did not produce improvement in avoidance or dissociative symptoms. In summary, there is little reason to select a benzodiazepine before other treatment alternatives. I have suggested elsewhere[9] three possible clinical indications for clonazepam: (1) acute stress reactions; (2) episodically in chronic PTSD when extreme anxiety interferes with the patient's participation in treatment; and (3) in carefully selected patients with comorbid alcohol or substance abuse (see also ref. 21).

Inositol

Inositol is a second messenger precursor that has been used successfully to treat both depression[26] and panic disorder[27] in randomized clinical trials. For those reasons, Kaplan and coworkers[28] conducted a randomized double-blind 4-week crossover study of inositol in 13 Israelis with PTSD related to military and civilian exposure to trauma. No difference was found between inositol and placebo (effect size .28), but some patients exhibited a reduction in depressive symptoms.

Antiadrenergic Agents: Propranolol and Clonidine

It is well established that adrenergic dysregulation is associated with chronic PTSD (see refs. 3 and 29 for details and references). Therefore, it is surprising that so few reports on PTSD treatment with clonidine or propranolol have been published despite the fact that positive findings with both drugs were reported as early as 1984.[30] Indeed, although there are no randomized clinical trials with either drug, there is one report[31] in which the beta-adrenergic blocking agent propranolol was administered to 11 physically and/or sexually abused children with PTSD in an A-B-A design (6 weeks off-6 weeks on-6 weeks off medication). Significant reductions in reexperiencing and arousal symptoms were observed during drug treatment, but symptoms relapsed to pretreatment severity following discontinuation of medication. In addition to Kolb *et al.*'s[30] open trial in which propranolol successfully reduced reexperiencing and arousal symptoms in Vietnam veterans, the only other relevant report is an unsuccessful open trial of propranolol in Cambodian refugees with PTSD.[32]

Three open trials have shown that the alpha$_2$-adrenergic agonist clonidine has produced successful outcomes in PTSD patients by reducing traumatic nightmares,

intrusive recollections, hypervigilance, insomnia, startle reactions, and angry outbursts, and by improving mood and concentration. It is noteworthy that each of these trials involved three different clinical populations with PTSD: Vietnam veterans,[30] abused children,[33] and Cambodian refugees.[34] In the latter study, a clonidine/imipramine combination was more effective than either drug alone.

Anticonvulsants

It has been proposed that following exposure to traumatic events, limbic nuclei become kindled or sensitized so that, henceforth, they exhibit excessive responsivity to less intense trauma-related stimuli. Post and associates[35] have written the most comprehensive and elegant review of this model. Arguing from this theoretical perspective, Lipper and associates[36] conducted an open trial of the anticonvulsant/antikindling agent carbamazepine with Vietnam veterans and observed significant reductions in traumatic nightmares, flashbacks, intrusive recollections, and insomnia. Since that time, positive results have been obtained in many open trials with anticonvulsant/antikindling drugs in PTSD patients. In five studies, carbamazepine produced reductions in reexperiencing and arousal symptoms, whereas in three studies, valproate produced reductions in avoidant/numbing and arousal (but not reexperiencing) symptoms (see ref. 21 for references).

An interesting recent clinical report described the effectiveness of a different anticonvulsant which was prescribed for a different theoretical reason. Vigabatrin, a specific gamma aminobutyric acid (GABA) transaminase inhibitor, is an effective anticonvulsant[37] that has been used to treat startle disease (hyperekplexia) of neonates.[38] Since fear-potentiated startle has been proposed as a psychobiologic mechanism for PTSD,[39] MacLeod[40] prescribed vigabatrin to five PTSD patients whose persistent startle and hypervigilance had not responded to other medications. In all cases, vigabatrin produced marked relief of these distressing symptoms.

It is always exciting when hypothesis-driven experiments yield successful results. It will be even more exciting if these open trials and case reports with anticonvulsants pass the test of randomized clinical trials.

Other Drugs

A number of other drugs have been the focus of one or two reports. Almost every kind of psychoactive drug has been represented and, as is usually the case with uncontrolled trials that get published, results have generally been positive. For the sake of completeness, I will mention each drug briefly. (The reader is referred to refs. 9 and 21 for further details and literature citations.)

Buspirone, an anxiolytic that is a 5-HT1A partial agonist, reduced reexperiencing and arousal symptoms in three patients. Cyproheptidine, a 5-HT antagonist, selectively suppressed traumatic nightmares without improving other PTSD symptoms. Lithium appeared to reduce hyperarousal symptoms in two open trials, with no therapeutic effect on reexperiencing or avoidant/numbing symptoms. One case report on phenothiazine treatment has appeared in which thioridazine reduced reexperiencing and arousal symptoms in one patient. Finally, the narcotic antagonist nalmefene markedly reduced

numbing symptoms in some patients but worsened anxiety and panic symptoms in others, whereas the narcotic antagonist naltrexone suppressed PTSD flashbacks in one patient.

These are interesting findings in view of current hypotheses about the pathophysiology of PTSD, but these drugs must be tested more rigorously before they can command our attention.

ANSWERS AND QUESTIONS

As stated at the outset, the answers provided by randomized clinical trials raise some important questions that must be addressed in subsequent research.

Have we been testing drugs on the wrong clinical populations? We have argued elsewhere (ref. 21, page 475) that:

> American Vietnam veterans who have served as subjects in most published randomized clinical trials may be the most severely impaired, chronic, and treatment-refractory patient cohorts. The reason why they remain the most available patients for drug trials is because they are still enrolled in VA treatment programs. . . [and] constitute a self-selected cohort of chronic patients with multiple levels of impairment who may be most refractory to drug (or any other) treatment.

TABLE 1 supports this conclusion. Considering an effect size of .5 standard deviations as the minimum effect size necessary for a clinically meaningful difference, every study that failed to exceed that threshold was conducted on military veterans. Comparing the civilian and veteran cohorts in the fluoxetine trial conducted by van der Kolk and coworkers,[4] the effect size for civilian (mostly female adult survivors of childhood sexual abuse) subjects was 1.12, whereas it was only .38 for military veterans who participated in the same protocol. The two brofaromine studies in which the same protocol was followed suggest the same conclusion. In the American trial[6] in which there was no difference between groups (effect size was only .13), 60% of the subjects were military veterans. In the mostly European trial,[7] considerably fewer (9% brofaromine and 26% placebo) subjects were military veterans;[7] results were nearly significant ($p \leq 0.08$) and the effect size was .71. In fact, the only study with military veterans that was both significant and clinically meaningful (effect size .70) was the trial of phenelzine conducted by Kosten and associates.[2] As the investigators in that study excluded all veterans with major depression, they may have inadvertently screened out the most treatment-refractory patients as well.

It is important to emphasize that I am not suggesting that there is anything about military trauma or male gender that is inherently refractory to pharmacotherapy. I am stating, however, that it would be premature to write off any drug as a potential treatment for PTSD until it has been tested on an appropriate clinical sample. Therefore, future studies should be conducted on a variety of patient cohorts to insure that lack of clinical success of a specific drug is genuinely due to lack of pharmacological efficacy rather than to the testing of a particularly refractory group of patients.

Have we optimized our clinical trials with respect to design and instrumentation? Kudler and associates[41] were the first to suggest that methodological factors such as differences in experimental design, duration of treatment, and instrumentation might account for differences in results from one clinical trial to the next. They emphasized

that the most successful trials (with MAOIs and TCAs) tended to last at least 8 weeks. This is generally true of the data shown in TABLE 1 with the notable exception of the 5-week fluoxetine trial on nonveteran subjects.[4]

Kudler *et al.*[41] also questioned the use of the Impact of Events Scale (IES) as the best instrument for assessing PTSD. The IES has served honorably in PTSD research, but it is a self-rating scale that neglects a whole category of PTSD symptoms (hyperarousal symptoms). There are many newer and more comprehensive self-report and observer rating scales that may be more sensitive for assessing weekly changes during a drug trial which are being used in the most current drug trials.[42] In fact, the IES itself was recently revised to correct some of its deficiencies.[43]

Research designs should also include adequate controls for psychiatric disorders frequently comorbid with PTSD, such as alcohol abuse/dependence, depression, and other anxiety disorders.[41] In this regard, the study by Brady *et al.*[12] is particularly noteworthy because it was designed to investige the efficacy of sertraline on patients comorbid for both PTSD and alcohol dependence.

Finally, all clinical trials have focused on reduction of PTSD symptoms as the major outcome measure. Although it is obviously important to monitor symptoms, other clinical domains such as social/vocational function or clinical utilization may be important outcomes, especially in patients with severe and chronic PTSD. It is conceivable that successful treatment with some cohorts might be indicated by improved marital, family, social, or vocational function or by lower inpatient or outpatient clinical service utilization, rather than by a reduction in PTSD symptoms.

Have we been testing the wrong drugs? Almost every drug tested in PTSD was developed as an antidepressant and has shown efficacy against panic and other anxiety disorders. Given high comorbidity rates between PTSD and such disorders and given the symptomatic overlap between PTSD, major depression, panic disorder, and generalized anxiety disorder,[44] it seems reasonable to test such drugs in PTSD. On the other hand, PTSD appears to be distinctive in a number of ways. First, it seems to be more complex than affective or other anxiety disorders; abnormalities have already been detected in at least seven unique neurobiological systems.[3] Second, its underlying pathophysiology appears to be different. For example, abnormalities in the hypothalamic-pituitary-adrenocortical (HPA) system, as shown by Yehuda and associates,[45] are markedly different from those present in major depressive disorder despite similarities in clinical phenomenology. In short, the time has come to develop and test drugs that have been developed specifically for PTSD rather than to recycle pharmacological agents that have been developed to treat affective or other anxiety disorders.

We have stated elsewhere that PTSD is the neurobiological and clinical consequence of failure of humans to cope with catastrophic stressors. During such exposure persons attempt to use the same neurobiological mechanisms that are activated by any stressful event. In contrast to a successful coping response which is followed by restoration of normal homeostatic balance, however, the unsuccessful coping that precipitates PTSD results in a steady state that deviates significantly from normal homeostasis. We have invoked McEwen's[46] concept of "allostasis" to describe this abnormal neurobiological steady state which we hypothesize to be present in PTSD patients.[47]

From this perspective, the best way to understand the pathophysiology of PTSD is by investigating the human stress response. Such an approach would focus attention on neuropeptides rather than biogenic amines. Because corticotropin-releasing factor (CRF) appears to play such a central role in the stress response,[48] it seems that drugs that block or modify the actions of CRF might prove efficacious in treating PTSD patients. This might include CRF antagonists such as alpha-helical CRF. Another approach is to enhance the actions of neuropeptide Y, a peptide that may act as an endogenous anxiolytic and that may diminish the actions of CRF.[48] Once we shift our focus from traditional antidepressants and anxiolytics to the complex human stress response, many other targets can be considered for potential anti-PTSD drugs. Hopefully, such a shift in focus will occur in the near future.

Are there different subtypes or stages of PTSD that may require different treatments at different times? Some evidence indicates that there may be different neurobiological subtypes of PTSD. For example, Southwick *et al.*[49] have shown that yohimbine may precipitate panic and flashbacks in some PTSD patients, whereas others are more likely to respond to *m*-chloro-phenyl-piperazine. This suggests that adrenergic dysregulation may be more prominent in some PTSD patients, whereas serotonergic sensitization is more prominent in others. This has obvious implications for pharmacotherapy.

Diagnostically we know that some traumatized patients develop borderline personality disorder or dissociative identity disorder or what Herman[50] has named, "complex PTSD," with or without PTSD itself. In the future we must determine if these also represent different subtypes of PTSD with a somewhat different pattern of neurobiological abnormalities that may require different pharmacotherapeutic strategies.

Finally, we must consider whether PTSD is a dynamic rather than a static disorder that evolves over time. Post and associates[35] presented such a model of PTSD which is based on mechanisms underlying sensitization and kindling. Sensitization and kindling evolve neurobiologically over time, and pharmacological responsivity to a drug (such as carbamezepine) may vary at different stages of evolution. Therefore, it would be essential to identify these different stages accurately in order to know when to prescribe a neuroleptic, an anticonvulsant, or some other drug. Extrapolating from this model, Post and associates[35] suggest that PTSD may also progress through different stages and that it may be necessary to identify these stages to know when to prescribe the most effective drug. One clinical vignette that is consistent with this theoretical approach was the finding by Katz *et al.*[7] that brofaromine was more effective in patients who had had PTSD for at least 12 months than in those who had developed PTSD within the last year.

Is there a magic bullet for PTSD? We concluded elsewhere[21] that no magic bullet for PTSD is in sight. Instead, we previously suggested that a combination of drugs, each targeting a specific cluster of symptoms, might provide the best approach at this time. For example, we recommended that MAOIs or TCAs might be best for reexperiencing, SSRIs for avoidant/numbing, and antiadrenergic agents (such as clonidine and propranolol) for hyperarousal symptoms.

Although that approach may be a reasonable for the time being, it is clear that we have just begun to conduct a systematic evaluation of drugs for PTSD. It is still an open question whether there is a specific drug or class of drugs that might provide

effective treatment for all three clusters of PTSD symptoms. The few randomized clinical trials that have been published have generated more questions than answers. We may not have tested drugs on the right clinical cohorts. We may not have used the best experimental protocols or assessment instruments. We may not have tested the most effective drugs. And we may not have understood how different subtypes or states of PTSD might affect the efficacy of different medications at different times.

In short, rather than feeling discouraged we should intensify our search for a magic bullet, fortified by recent gains in our emerging understanding of the pathophysiology of PTSD.

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